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ARMY MEDICAL RESEARCH INST OF INFECTIOUS DISEASES FR--ETC F/G 6/3  
PROTEIN SPARING THERAPY DURING PNEUMOCOCCAL SEPSIS IN RHESUS MO--ETC(U)  
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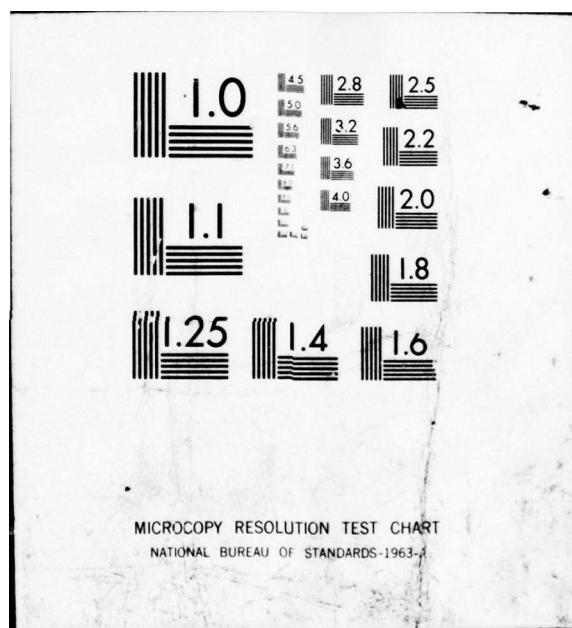
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6 Protein Sparing Therapy during Pneumococcal Sepsis in Rhesus Monkeys. 2

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In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on the Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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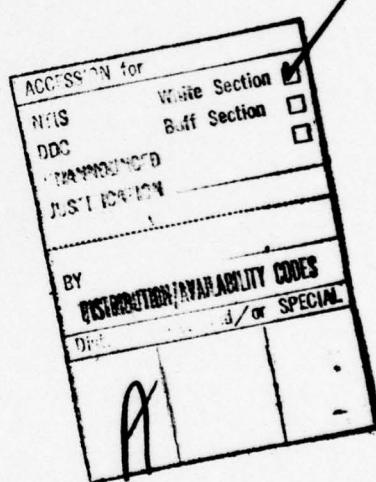
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## ABSTRACT

A model was developed in the rhesus monkey to determine if the marked wasting of body proteins associated with sepsis could be prevented by an intravenous supply of various nutritional substrates. All monkeys were given a basic infusion of 0.5 g of amino acid nitrogen/kg body weight via an indwelling catheter in the jugular vein. Three groups were given either no added calories, 85 cal/kg from dextrose, or 85 calories from lipid. In each dietary group six monkeys were inoculated with  $3 \times 10^8$  Streptococcus pneumoniae and four monkeys, heat-killed organisms. In the monkeys infused with the amino acids alone, pneumococcal sepsis resulted in a four-fold increase in loss of body proteins, compared to calorie-restricted controls. Addition of 85 cal/kg/day of either dextrose or lipid markedly reduced body wasting associated with infectious disease. The calories from lipid were utilized by the septic host as a source of energy, with a slightly reduced efficiency, when compared to the isocaloric infusion of dextrose. The nitrogen sparing of the fat emulsion could not be accounted for by its glycerol content. Therefore, the septic monkey seemed to utilize fatty acids as an energy substrate. It appeared that the carbohydrate calories tended to favor the synthesis of peripheral proteins (associated mainly with skeletal muscle), while lipid calories favored synthesis of visceral proteins, such as plasma albumin and acute-phase proteins.

It has been well documented that severe sepsis in man or experimental animals results in marked wasting of body proteins which can lead to rapid development of a protein-calorie malnutrition syndrome.<sup>1,2</sup> The wasting of body protein permits a flux of amino acids from tissues such as skeletal muscle and skin to the viscera where the amino acids are utilized for gluconeogenesis; synthesis of a large variety of proteins involved in specific and nonspecific host defense mechanisms against infectious disease, acute-phase proteins, the production of a new white cells, and obligatory proteins necessary to maintain the homeostasis of the host; and utilization as a direct source of energy.<sup>3</sup> Some investigators have suggested that increasing the caloric intake during certain bacterial infections in man could reduce the wasting of body proteins.<sup>4</sup> However, anorexia is a common symptom of most infectious illnesses,<sup>1,2</sup> which complicates the evaluation of oral nutrition in septic man and experimental animals.

An intravenous infusion of amino acids has been shown to be of value and is able to spare body protein.<sup>5-8</sup> However, conflicting data have been reported on the ability of the critically ill patient to utilize infused lipid emulsions as a caloric source. A number of investigators have reported that the intravenous lipid emulsion encourages nitrogen retention, weight gain, wound healing, and closure of enteric fistulas in surgical and traumatized patients.<sup>9-14</sup> However, other investigators<sup>15,16</sup> have failed to observe any reduction in nitrogen sparing in thermally injured patients infused with large doses of soybean fat emulsion. Further, results from various experimentally induced infections in rats and monkeys have suggested that during sepsis, they were unable to develop "starvation ketosis" or

to clear rapidly an oral or intravenous lipid load.<sup>1/20</sup> These various observations raised the question as to whether the septic patient would be able to utilize fatty acids as an efficient caloric substrate.

To help determine whether various substrates could prevent the wasting of body proteins during sepsis, techniques were adapted from clinical studies in man to develop a parenteral nutrition model in the rhesus monkey. During pneumococcal sepsis, monkeys were infused via a central venous catheter with a constant amount of amino acid nitrogen with or without added isocaloric amounts of either dextrose or a lipid emulsion. These studies indicate that the wasting of body proteins during sepsis could be prevented by the infusion of amino acids together with an adequate supply of nonprotein calories from either dextrose or fat.

#### METHODS

Forty-eight male rhesus monkeys (*Macaca mulatta*), weighing three to five kilograms, were adapted to chair-restraint for three days. Only those monkeys observed to be eating normally, maintaining their body weight, having normal white blood count and clinical chemistry, and showing no tendencies for excessive hyperactivity were accepted into the study.

After adaptation to restraint in metabolic chairs, the monkeys were anesthetized with 10 mg/kg of Ketamine\* and prepared for surgery. As described previously<sup>21</sup> silastic catheters were implanted in the internal jugular vein and carotid artery under sterile surgical techniques and tunneled to the upper-center scapular area for exit. A polyethylene catheter was also placed in the femoral vein. The jugular catheter was

## FOOTNOTE

\* Parke-Davis & Co.

inserted at the approximate point where the jugular vein joins the vena cava and was utilized for the infusion of nutrient solution. The carotid catheter was inserted to the level of the aortic arch and was utilized to obtain arterial samples. The femoral vein catheter was inserted into the caudal vena cava just proximal to bifurcation of the iliac veins, and was utilized to obtain venous blood samples from the lower hind-quarters. The carotid artery and femoral vein catheters were kept patent by infusion (0.5 ml/hr of 0.5 percent saline which contained 0.5 units/ml of heparin).

After surgery the monkey was returned to a metabolic chair so that quantitative urine and fecal collections could be made. The catheters were connected under sterile conditions to three-way stopcocks and placed in a sterile plastic "glove" box that contained gauze saturated with Prepodyne (Poloxamer-iodine complex\*). The monkeys were then infused via the jugular catheter with 0.5 percent sodium chloride (100-120 ml/kg/day) until 0800 hours the next day. On the day after surgery a test solution was infused via the jugular vein; it supplied 0.5 g/kg/day of amino acid nitrogen<sup>†</sup> (FreAmine II), with or without 85 cal/kg/day of nonprotein calories plus electrolytes, trace elements, and vitamins.<sup>21</sup> Infusion rates were metered by i.v.-infusion pump \*\*. Each pump was calibrated at the beginning and end of the experiment to assure the accuracy of the infusion rate.

The monkeys were assigned to one of three experimental groups as follows: one was infused with a solution that supplied 0.5 g of amino acid nitrogen/kg/day; the second consisted of the same amino acid solution plus 85 cal/kg/day from dextrose<sup>†</sup>; and the third consisted of

## FOOTNOTES

\* West Chemical Products, Inc.

† McGaw Laboratories

\*\* IVAC-500 Pump, IVAC Corp.

the amino acids plus 85 cal/kg/day from a 10 percent fat emulsion\*.

The infusion rate of the intralipid was regulated by a separate IVAC pump and was mixed with the amino acid solution in a "T" connector<sup>+</sup>, which was held in a sterile glove box. Monkeys were assayed on a pair-weight basis into a group, so that the average starting weights were similar for each group.

At 1000 hours on the day after starting the infusion of the parenteral nutritional solution, the monkeys were injected via the femoral vein with  $3 \times 10^8$  live or heat-killed Streptococcus pneumoniae, type I, strain A5. Monkeys injected with heat-killed organisms served as controls.

Monkeys injected with the live organisms became febrile; all had pneumococcal septicemia and elevated white blood counts by day two after exposure. At this time, both the septic and control monkeys were started on therapy with penicillin (300,000 units i.m./day).

Eighteen percent of the monkeys injected with the live organisms died before the end of the experiment, and were evenly distributed among the dietary groups. At autopsy it was determined that pneumococcal meningitis and overwhelming pneumococcal septicemia were the causes of death. The remainder of the septic monkeys had lysis of fever and negative blood cultures by the third day after beginning antibiotic treatment and they, along with the control monkeys, had their catheters removed and cultured at that time.

Immediately after starting the infusion of the parenteral nutrition solution each monkey was administered a red stool marker by an intragastric bolus of 3 ml of an oral suspension of pyrvinium pamoate\*\*. Twenty-four-hour urine and red feces collections were made on each

## FOOTNOTES

\* Intralipid, Cutter Laboratories

† Abbott Laboratories

\*\* Parke-Davis

monkey for the next six days. Twenty-four-hour urine volumes were recorded; a specimen was analyzed for pH, glucose, protein, and ketones by dip stick\*; samples were frozen at -20° for future analyses. Fecal samples were placed in plastic 50-ml graduated tubes, digested for 24 hours with 2 ml of sulfuric acid, diluted to 25 ml, and homogenized for 30 seconds in a Polytron<sup>†</sup>. Samples of urine, feces, and nutrient solutions were analyzed for total nitrogen by automated procedures.<sup>22</sup> In addition,  $\beta$ -hydroxybutyrate<sup>23</sup> and creatinine<sup>24</sup> were determined by automated procedures.

A zero-time fasting blood sample was obtained immediately before starting the nutrient infusion solution and additional samples were taken on days 1-3 and 6. The blood was cultured and white blood cell counts were made. Plasma was separated from the blood and analyzed for  $\beta$ -hydroxybutyrate,<sup>23</sup> free fatty acids,<sup>25</sup> cholesterol,<sup>26</sup> triglycerides<sup>26</sup> by automated procedures, insulin, by radioimmunoassay,<sup>27</sup> and albumin and haptoglobin by an automated immunoprecipitin system.<sup>28</sup> Hours of fever were calculated as the product of degrees F greater than 100 F multiplied by duration in hours.

A monkey was dropped from the study if he succumbed to the infection, removed the catheter, or developed catheter sepsis. Catheter sepsis was defined as the presence of organisms other than S. pneumoniae in blood or catheter cultures. This occurred in only one monkey throughout the study. Six septic and four nonseptic (control) monkeys in each group met the criteria and were included for final calculations. For sequential analysis within a group, data were analyzed by paired one-way analysis of variance. Intergroup comparisons were made by

## FOOTNOTES

\* Multi-Stix, Ames Co.

† Brinkman Corp.

one-way analysis of variance. A p value of less than 0.05 was considered significant under the null hypothesis.

#### RESULTS

When infused with the amino acids alone, the urinary nitrogen excretion exceeded the intake, resulting in a negative nitrogen balance in control monkeys receiving the heat-killed organisms (Fig. 1). In contrast, septic monkeys significantly increased their urinary nitrogen excretion to almost twice that seen in the noninfected controls.

The addition of 85 cal/kg/day of dextrose to the amino acid solution in control monkeys resulted in urinary nitrogen excretion, which was less than intake, resulting in positive nitrogen balance which was maintained for the six days of the study (Fig. 2). Nitrogen excretion was slightly but significantly increased during the febrile phase of the infection, but this elevation was markedly less than seen in septic monkeys given the amino acids alone (Fig. 2).

The infusion of 85 cal/kg/day of Intralipid plus amino acids in control monkeys resulted in urinary nitrogen excretion which was slightly less, or equivalent to, nitrogen intake (Fig. 3). During illness in septic monkeys infused with lipids and amino acids, urinary nitrogen excretion was elevated, but again it was not as marked as that observed when the monkeys were infused with amino acids alone (Fig. 3).

The cumulative nitrogen balance over the six-day period for control and septic monkeys receiving three different nutritional support solutions are summarized in Fig. 4. By assuming that a monkey contains 13 percent protein with 16 percent nitrogen, it was calculated that the

control monkeys, infused with amino acids alone, lost approximately 2 percent of their body proteins in the six days. In contrast, septic monkeys lost almost 11 percent of their body proteins over the same period, an amount significantly greater than that observed in control monkeys infused with amino acids alone.

When dextrose was added to the amino acid solution, the control monkeys accumulated nitrogen equivalent to almost 2.4 percent of their initial body protein. With this solution the septic monkeys went into a slight negative balance during the febrile phase of the study, but overall for the six-day period, gained nitrogen, equivalent to 1.1 percent of their initial body proteins, an amount not significantly different from that observed in the control monkeys given the same infusion.

When the amino acids were supplemented with lipids, control monkeys gained nitrogen at an equivalent to 1.2 percent of their initial body protein. Septic monkeys given this diet lost nitrogen during the febrile phase of the illness. This amounted to a cumulative loss of only 1.6 percent. Nitrogen retention was best in control monkeys infused with amino acids plus dextrose, slightly less when infused with amino acids alone. However, differences between these groups were not significant when compared by one-way analysis of variance. In contrast, septic monkeys fed amino acids alone exhibited significantly greater losses of body protein than did septic monkeys fed amino acids plus lipid or amino acids plus dextrose. The slightly better nitrogen retention in the septic monkeys fed amino acids plus dextrose was not significantly different from that of the monkeys fed the amino acid plus lipid.

When infused with the amino acids alone the control monkeys excreted approximately 1 mmole/kg/day of  $\beta$ -hydroxybutyrate, indicating that they had developed starvation ketosis (Fig. 1). In contrast, urinary  $\beta$ -hydroxybutyrate concentrations markedly decreased in septic monkeys. The plasma  $\beta$ -hydroxybutyrate and free fatty acids both decreased in infected monkeys when compared to fasted values and there was a small but significant increase in peripheral insulin on the first day after inoculation with virulent S. pneumoniae (Fig. 5). When compared to fasted values (zero time), no significant changes were observed in plasma  $\beta$ -hydroxybutyrate, free fatty acids, or insulin values in the control monkeys infused with the amino acids alone.

The infusion of dextrose plus amino acids almost completely inhibited the excretion of urinary  $\beta$ -hydroxybutyrate (Fig. 2) and resulted in a marked drop in its plasma level and free fatty acids in both control and septic monkeys (Fig. 6). At the same time plasma insulin concentrations were increased almost ten-fold.

In control monkeys infused with amino acids plus lipid, urinary  $\beta$ -hydroxybutyrate excretion was maintained at fasting ketotic concentrations (Fig. 3). In contrast, during illness its excretion rate was significantly decreased. The infusion of lipid increased both free fatty acid and  $\beta$ -hydroxybutyrate concentrations in the plasma of control monkeys (Fig. 7). This appeared to take place even though the plasma insulin values were slightly elevated. In the septic monkeys, free fatty acids were elevated to an even greater degree and  $\beta$ -hydroxybutyrate concentrations were the same or slightly above those seen in fasted monkeys. Plasma insulin values were only slightly elevated on the day after inoculation with live organisms.

Both control and septic monkeys developed marked hypertriglyceridemia and hypercholesterolemia when infused with the amino acids plus lipid. These increases were significantly more severe in the septic group (Table I). When compared to fasting values (zero time), plasma triglycerides were slowly but significantly elevated in both control and septic monkeys infused with amino acids alone, while plasma cholesterol tended to decrease in the septic monkeys. The addition of dextrose to the amino acid mixture maintained plasma triglycerides at fasting values in both the control and septic monkeys. However, plasma cholesterol tended to decrease in the infected group.

The infusion of amino acids alone resulted in a gradual decrease in plasma albumin, which was more marked in the septic group (Table II). The addition of dextrose to the amino acids also resulted in a gradual decrease in plasma albumin but no difference was noted between control and septic monkeys. When lipid was added to amino acids, no significant drop in plasma albumin was observed in either the control or infected group. Plasma haptoglobin was slightly elevated by the second day after surgery in the control monkeys with no difference observed among the three dietary groups. In contrast, plasma haptoglobin was progressively elevated to high concentration following exposure to living S. pneumoniae in all three dietary groups. However, the rate of increase was significantly slower in the amino acid plus dextrose monkeys compared to the increases seen in the septic monkeys receiving amino acids alone or amino acids plus lipid (Table II).

## DISCUSSION

Chaired, nonseptic rhesus monkeys can be maintained in positive nitrogen balance and gain weight when infused via a central venous catheter with 0.5 g of nitrogen and 100 cal/kg/day.<sup>21</sup> When noninfected monkeys were infused with this amount of amino acids alone, they went into a slightly negative nitrogen balance and became keto-adapted. While the group as a whole lost approximately 2 percent of their body protein over the six-day experimental period, some of the monkeys were in a slight positive balance, so that the loss was not statistically different from monkeys fed amino acids plus the added calories. These observations support the concept that amino acid infusion promotes protein sparing in the traumatized patient who becomes "keto-adapted."<sup>5-8,18,29</sup> During pneumococcal sepsis, the monkeys maintained on amino acids alone went into marked negative balances and had a severe reduction in urinary and plasma ketone concentrations. The addition of 85 cal/kg/day from either dextrose or lipid to the amino acid solution resulted in a marked reduction in the loss of body nitrogen.

The addition of 85 cal/kg/day of dextrose maintained nonseptic monkeys in positive balance throughout the six-day study. Further, the dextrose caused a ten-fold increase in peripheral insulin concentrations, which effectively inhibited lipolysis and ketosis. Thus, in the monkey receiving amino acids plus dextrose the calorie expenditure was met almost completely by the nutrient infusion. During pneumococcal sepsis, however, urinary nitrogen excretion was significantly increased, suggesting that the infectious process elevated the calorie requirements, which the monkey met by breaking down and oxidizing body proteins.

These observations support the conclusions that infection and sepsis do increase energy requirements.<sup>4,30,31</sup>

Dextrose appeared to be a slightly more efficient calorie substrate than lipid. This, in part, may be related to the reduced ketone body production<sup>17,18,32</sup> and plasma lipid-disposal acitivity<sup>20</sup> associated with various types of infections. The reduced urinary  $\beta$ -hydroxybutyrate and elevated plasma triglyceride concentrations in septic monkeys receiving the amino acid and lipid combination support these conclusions. However, the overall protein loss was not statistically greater than that observed in the septic monkeys fed amino acids plus dextrose. These observations on the ability of the septic host to utilize lipids as a calorie source are in agreement with a number of investigators.<sup>9-14</sup>

In contrast, Long et al<sup>15</sup> reported that critically ill or severely burned patients were unable to utilize lipid for protein-sparing, while McDougal, Willmore, and Pruitt<sup>16</sup> suggested that the glycerol content of the fat emulsion was the major calorie source utilized by burned patients. Similarly Brennan and co-workers<sup>33</sup> concluded that the nitrogen-sparing associated with infusion of fat emulsion in fasting man was associated with the glycerol content of this solution. The glycerol present free in the solution or as a part of the tryglycerides, represents approximately 13 percent of the caloric value of the fat emulsion (soybean oil suspended in glycerol) or about 10 cal/kg/day in these studies. In preliminary experiments in our laboratory (RWW), the addition of 32 cal/kg/day of dextrose to the amino acid solution was not as effective in preventing nitrogen wasting in the septic monkey as was the infusion of 85 cal of Intralipid, the fat emulsion. Since this fat emulsion supplies only ten calories of glycerol, it indicated that

during pneumococcal sepsis in the rhesus monkey was able to utilize fatty acids as an energy substrate. However, the elevated triglycerides, cholesterol and free fatty acids in the plasma of the septic monkey suggest that the infectious process resulted in some alterations in: the ability to hydrolyze the soybean oil, metabolism of fatty acids, and rates of utilization of the resultant two carbon fragments for synthesis of ketones, cholesterol, and fatty acids.

Despite the nitrogen retention observed in septic and nonseptic monkeys infused with the amino acids plus dextrose, the plasma serum albumin concentrations declined over the six-day experimental period. Further, the accumulation of haptoglobin (an acute-phase protein<sup>28</sup>) was at a slower rate in septic monkeys infused with amino acids plus dextrose than in the other groups. It is well established that insulin stimulates both sequestering of amino acids in the muscle and synthesis of muscle proteins.<sup>34</sup> Thus, it is interesting to speculate that the ten-fold increase in peripheral insulin values observed in monkeys infused with amino acids plus dextrose resulted in a flow or sequestering of amino acids in skeletal muscle and away from the visceral cells responsible for serum protein synthesis and immune functions. The reversed flow of amino acids away from skeletal muscle may be occurring in the monkeys infused with amino acids or amino acids plus lipids. Indeed, preliminary reports have suggested that infusion of isotonic amino acids improved albumin synthesis rate<sup>35</sup> and immune function.<sup>36</sup>

Despite the problems of requiring chair-restraint and relatively small sample size, the rhesus monkey model utilized in these studies provides useful data which can be applied to the problems of intravenous alimentation of critically ill patients. The model has an advantage

over clinical studies, in that the effects of infection can be evaluated in a subject who is not compromised by other problems, such as injury, surgical procedures, radiation, chemotherapy, or organ failure. It is also possible to evaluate nutritional support which may not be the most advantageous for the monkey's defense against infectious disease.

In the present study, S. pneumoniae was chosen as the infectious organism because it is a gram-positive bacterium which does not produce a toxin, will remain in the extracellular spaces, and the resulting clinical illness from exposure to this organism has been well characterized in the rhesus monkey.<sup>20</sup> It has been reported<sup>19,20</sup> that a gram-negative organism which is an endotoxin-producer such as Salmonella typhimurium, will have more marked effects on host lipid metabolism than the gram-positive S. pneumoniae. Therefore, future research efforts will utilize gram-negative toxin-producing bacteria, intracellular bacteria, and viruses in the monkey model, to determine whether the etiology of the infectious organism can alter the host's ability to utilize the infused substrates especially the lipid emulsion.

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TABLE I  
SEQUENTIAL CHANGES IN PLASMA TRIGLYCERIDES AND CHOLESTEROL

Treatment	Live <u>S. pneumoniae</u> (n=6)						Heat-killed <u>S. pneumoniae</u> (n=4)					
	D-0			D-1			D-2			D-3		
	Triglycerides (mg/dl)			D-0			D-1			D-2		
Amino acids	28	48	48*	53*	53*	41	46	55	63*	63*		
	± 3	± 5	± 7	± 21	± 17	± 24	± 15	± 22	± 24	± 28		
Amino acids + Dextrose	18	15	18	38	19	19	16	30	38	39		
	± 12	± 3	± 9	± 24	± 9	± 8	± 11	± 19	± 15	± 15		
Amino acids + Lipid	15	334*	979*†	1063*†	571*	7	173*	268*	263*	223*		
	± 6	± 136	± 282	± 310	± 261	± 7	± 52	± 89	± 69	± 25		
Cholesterol (mg/dl)												
Amino acids	124	128	111	93*	96*	131	125	133	125	120		
	± 13	± 13	± 8	± 11	± 12	± 10	± 15	± 23	± 28	± 19		
Amino acids + Dextrose	104	85	80*	72*	58*†	91	98	83	79	89		
	± 5	± 12	± 8	± 7	± 9	± 3	± 10	± 8	± 10	± 12		
Amino acids + Lipid	113	196*	312*	380*	490*†	136	200*	272*	298*	355*		
	± 7	± 17	± 30	± 30	± 62	± 12	± 11	± 34	± 36	± 36		

\* p < 0.05 compared to zero time.

† p < 0.05 compared to heat-killed.

TABLE II  
SEQUENTIAL CHANGES IN PLASMA ALBUMIN AND HAPTOGLOBIN

Treatment	Live <u>S. pneumoniae</u> (n=6)						Heat-killed <u>S. pneumoniae</u> (n=4)					
	D-0	D-1	D-2	D-3	D-6	Mean $\pm$ S.E.	D-0	D-1	D-2	D-3	D-6	
Albumin (g/dl)												
Amino acids	3.01	2.69*	2.61*	2.17*†	2.08*†	3.17	2.76*	2.66*	2.63*	2.63*	2.64*	
	$\pm$ 0.09	$\pm$ 0.09	$\pm$ 0.08	$\pm$ 0.10	$\pm$ 0.10	$\pm$ 0.11	$\pm$ 0.14	$\pm$ 0.12	$\pm$ 0.08	$\pm$ 0.08	$\pm$ 0.23	
Amino acids +	2.86	2.42*	2.32*	1.86*	1.91*	2.95	2.62*	2.45*	2.44*	2.44*	2.27*	
Dextrose	$\pm$ 0.07	$\pm$ 0.10	$\pm$ 0.09	$\pm$ 0.11	$\pm$ 0.12	$\pm$ 0.08	$\pm$ 0.09	$\pm$ 0.06	$\pm$ 0.15	$\pm$ 0.15	$\pm$ 0.14	
Amino acids +	2.46	2.54	2.39	2.49	2.39	2.45	2.55	2.40	2.46	2.46	2.61	
Lipid	$\pm$ 0.14	$\pm$ 0.15	$\pm$ 0.14	$\pm$ 0.10	$\pm$ 0.08	$\pm$ 0.22	$\pm$ 0.13	$\pm$ 0.10	$\pm$ 0.08	$\pm$ 0.08	$\pm$ 0.10	
Haptoglobin (mg/dl)												
Amino acids	105	127*	148*†	157*†	173*†	91	109	101	101	101	97	
	$\pm$ 17	$\pm$ 15	$\pm$ 20	$\pm$ 15	$\pm$ 14	$\pm$ 16	$\pm$ 17	$\pm$ 7	$\pm$ 16	$\pm$ 16	$\pm$ 18	
Amino acids +	66	83	94*	117*	143*†	77	95	96	94	94	101	
Dextrose	$\pm$ 11	$\pm$ 4	$\pm$ 11	$\pm$ 3	$\pm$ 9	$\pm$ 9	$\pm$ 16	$\pm$ 15	$\pm$ 17	$\pm$ 17	$\pm$ 18	
Amino acids +	70	102*	112*	142*†	187*†	90	111*	113*	112*	112*	109*	
Lipid	$\pm$ 17	$\pm$ 12	$\pm$ 16	$\pm$ 10	$\pm$ 16	$\pm$ 4	$\pm$ 7	$\pm$ 4	$\pm$ 5	$\pm$ 5	$\pm$ 6	

\*  $p < 0.05$  compared to zero time.

†  $p < 0.05$  compared to heat-killed.

## FIGURE LEGENDS

Fig. 1: Sequential changes in urinary nitrogen and  $\beta$ -hydroxybutyrate of monkeys infused with amino acids. Values are the mean + S.E. of six monkeys in the septic group or four monkeys in the control group. The horizontal dashed line is the mean nitrogen intake (NI).

Fig. 2: Sequential changes in  $\beta$ -hydroxybutyrate and urinary nitrogen excretion of monkeys infused with amino acids plus dextrose. Values are the mean + S.E. for six septic or four control monkeys. The horizontal dashed line is the mean nitrogen intake (NI) for each group.

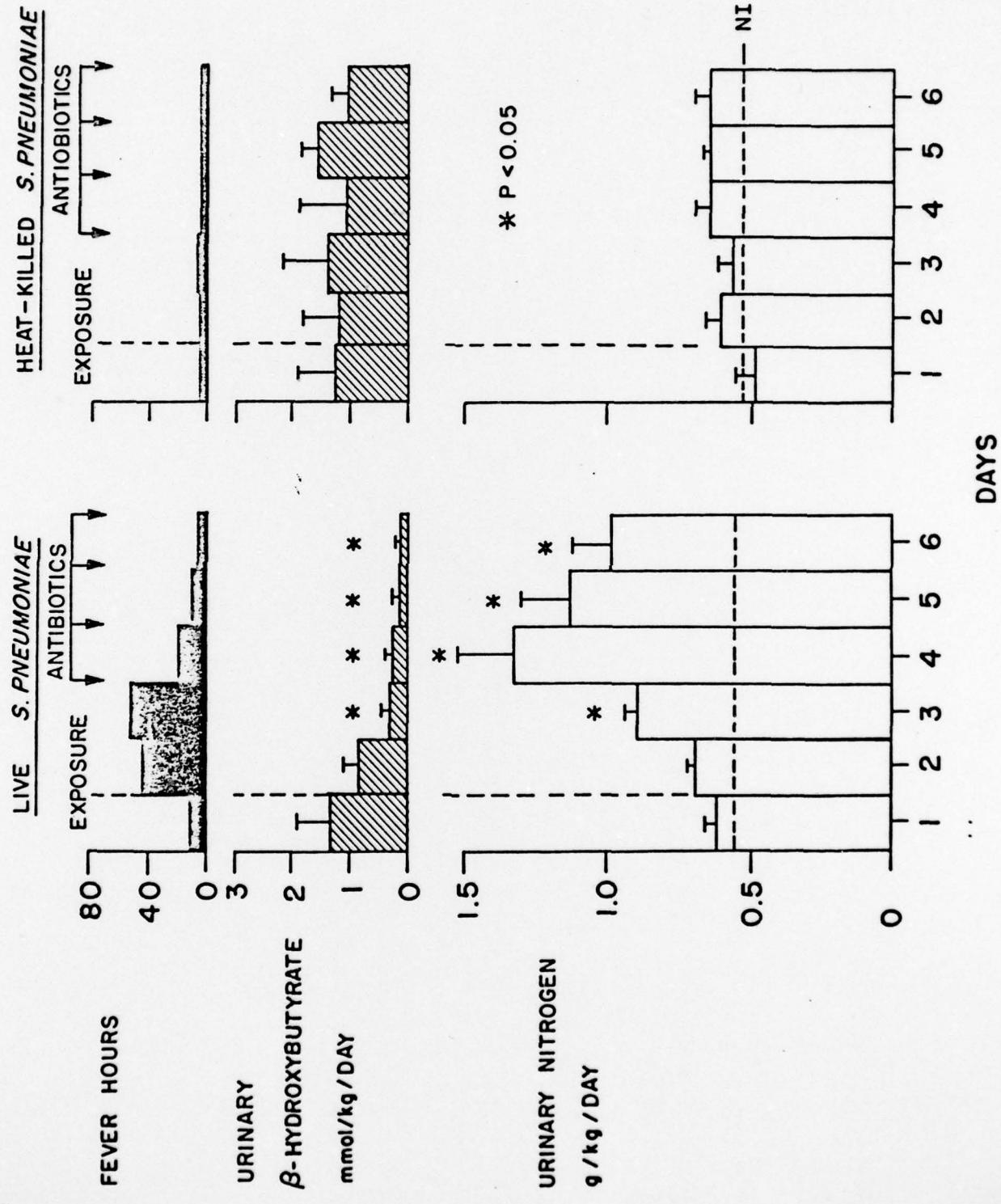
Fig. 3: Sequential changes in urinary  $\beta$ -hydroxybutyrate and nitrogen excretion of monkeys infused with amino acids plus lipid emulsion. Values are the mean + S.E. of six septic or four control monkeys. The horizontal dashed line represents the mean nitrogen intake (NI) for each group.

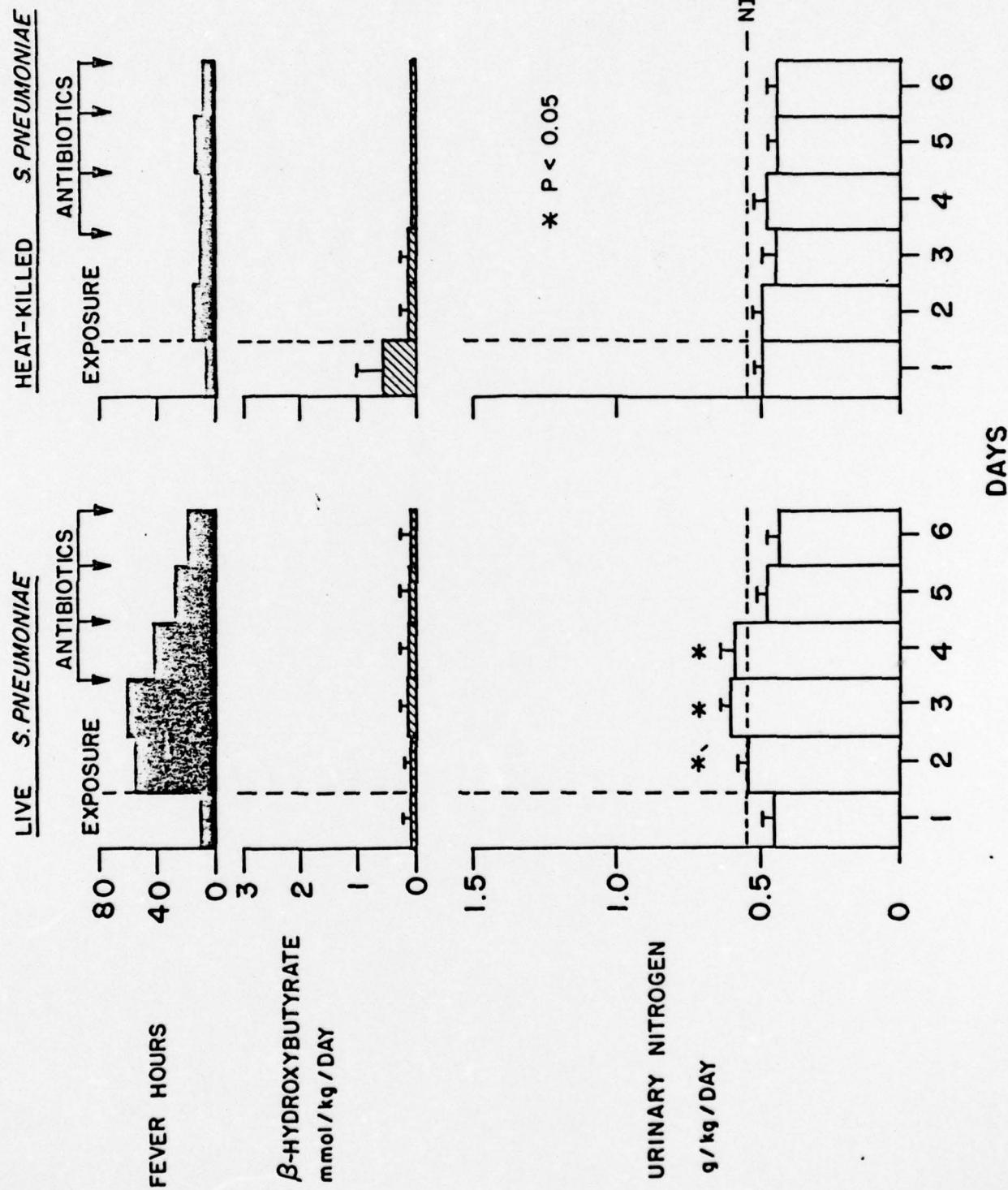
Fig. 4: Cumulative nitrogen balance over the six-day period for heat-killed controls (black area) and septic (hashed area) monkeys receiving either amino acids alone, amino acids and dextrose, or amino acids and lipid emulsion.

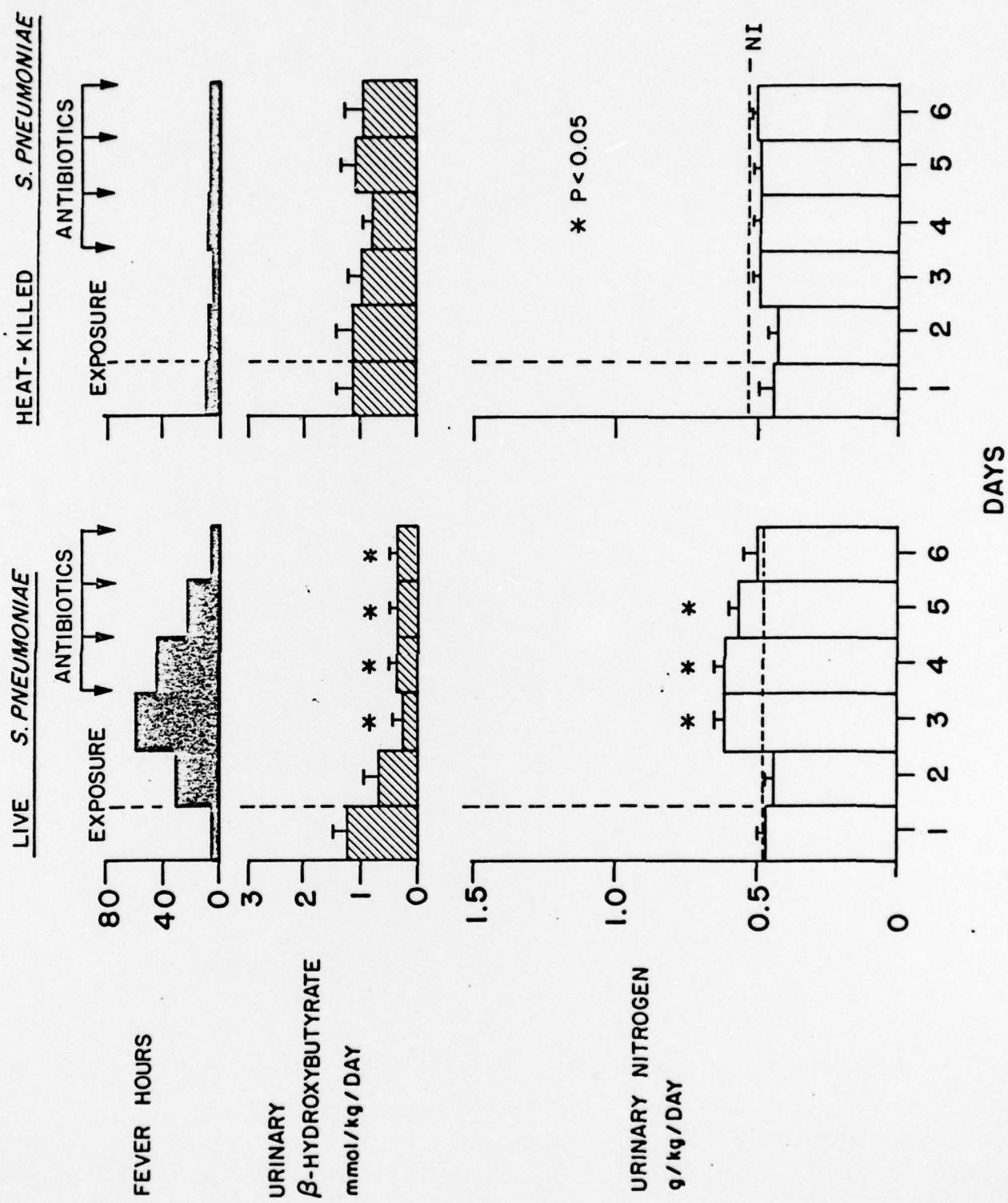
Fig. 5: Sequential changes in plasma  $\beta$ -hydroxybutyrate, free fatty acids, and insulin in monkeys infused with amino acids. Each value is the mean  $\pm$  S.E. of six septic or four control monkeys.

Fig. 6: Sequential changes in plasma  $\beta$ -hydroxybutyrate, free fatty acids, and insulin in monkeys infused with amino acids plus dextrose. Each value is the mean  $\pm$  S.E. of six septic or four control monkeys.

Fig. 7: Sequential changes in plasma  $\beta$ -hydroxybutyrate, free fatty acids, and insulin in monkeys infused with amino acids plus lipid emulsion. Each value is the mean  $\pm$  S.E. of six septic or four control monkeys.

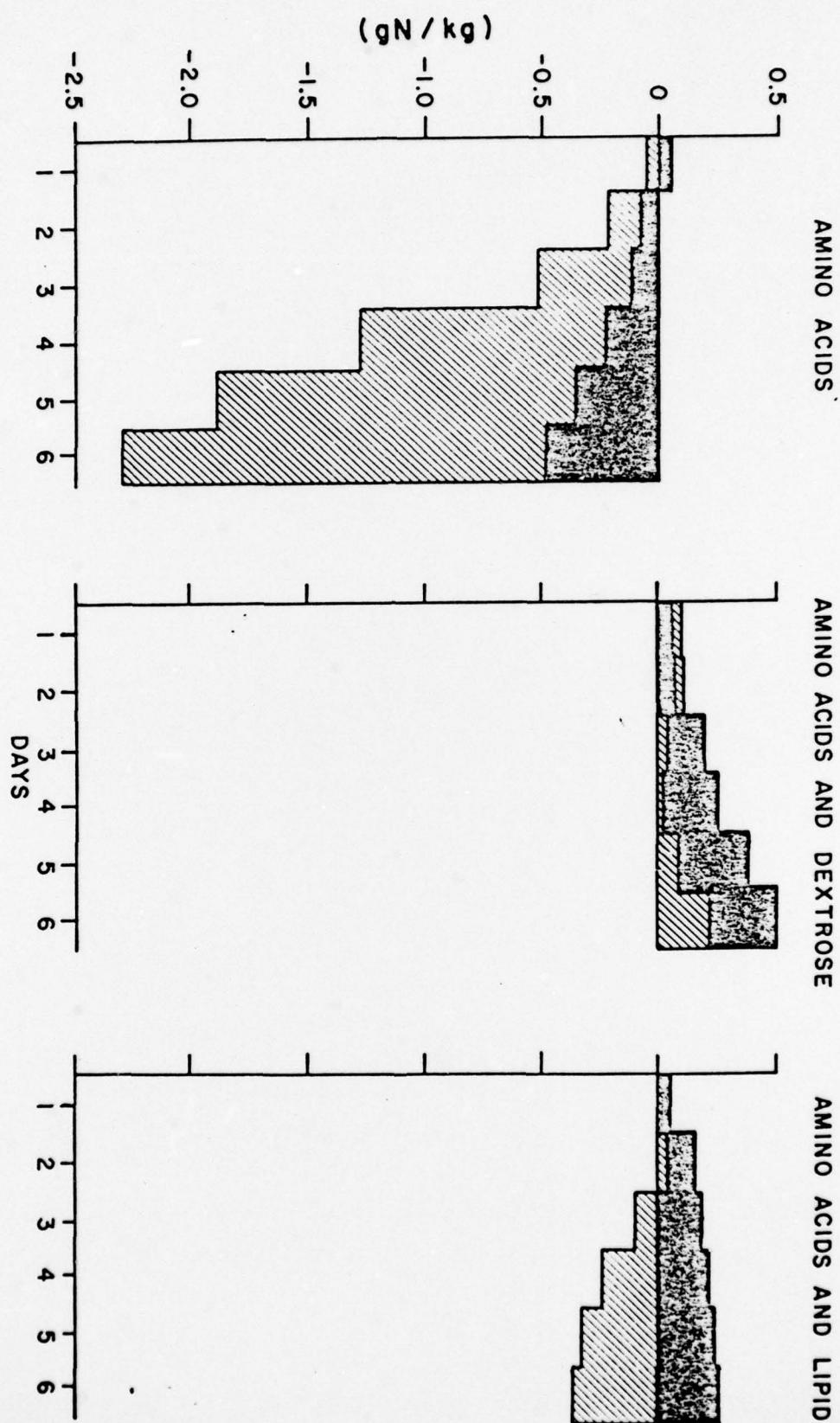






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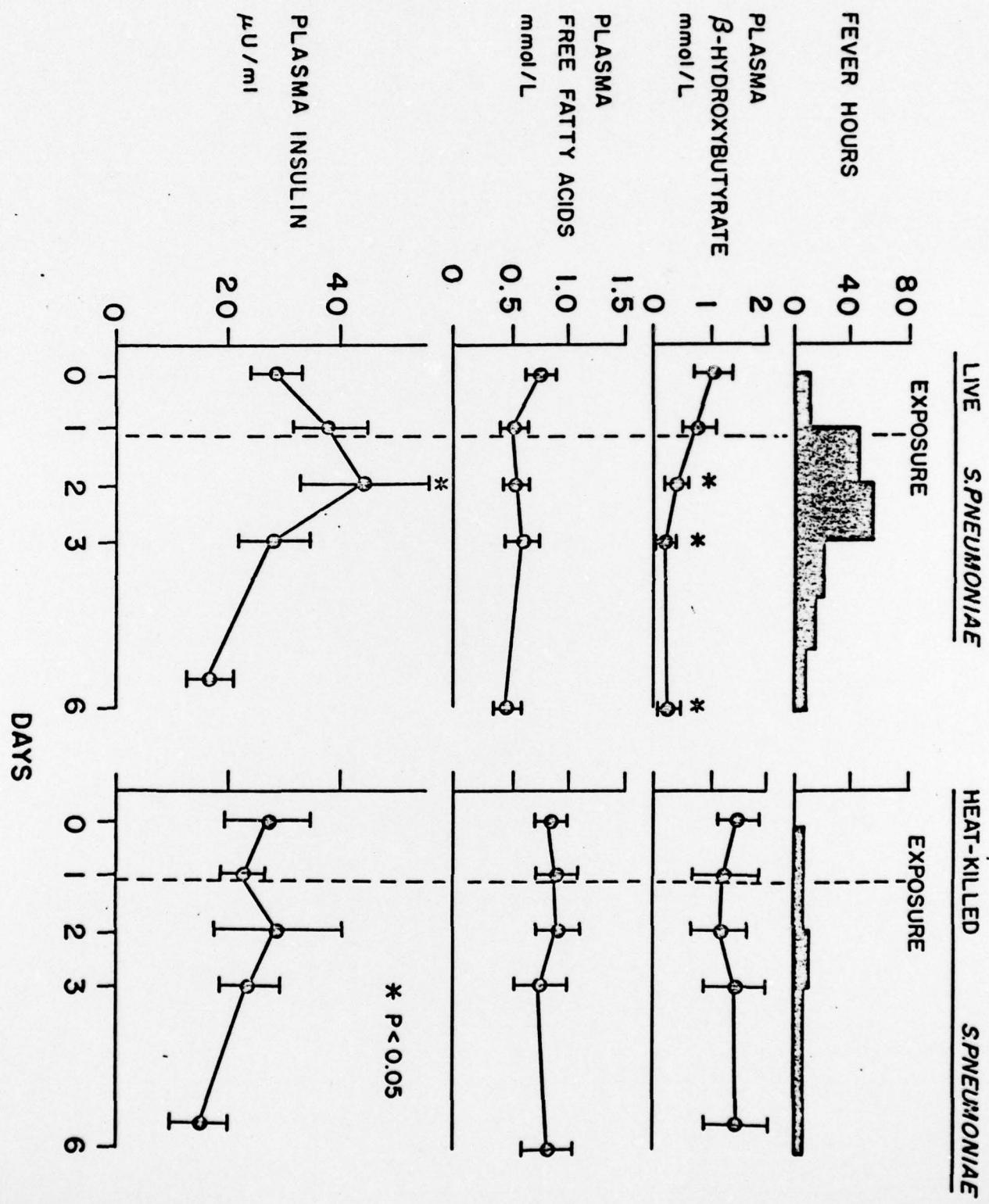


Fig 6

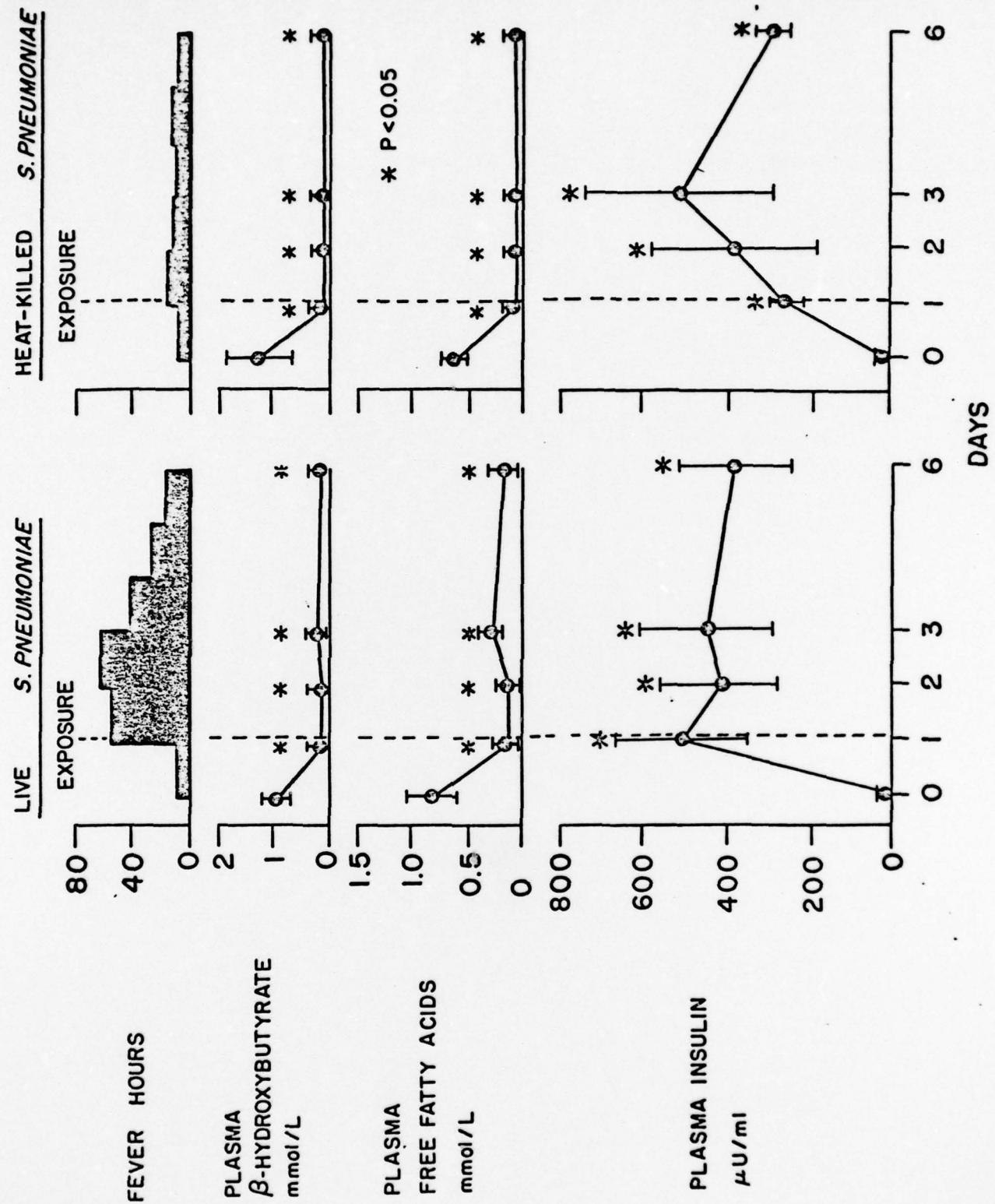
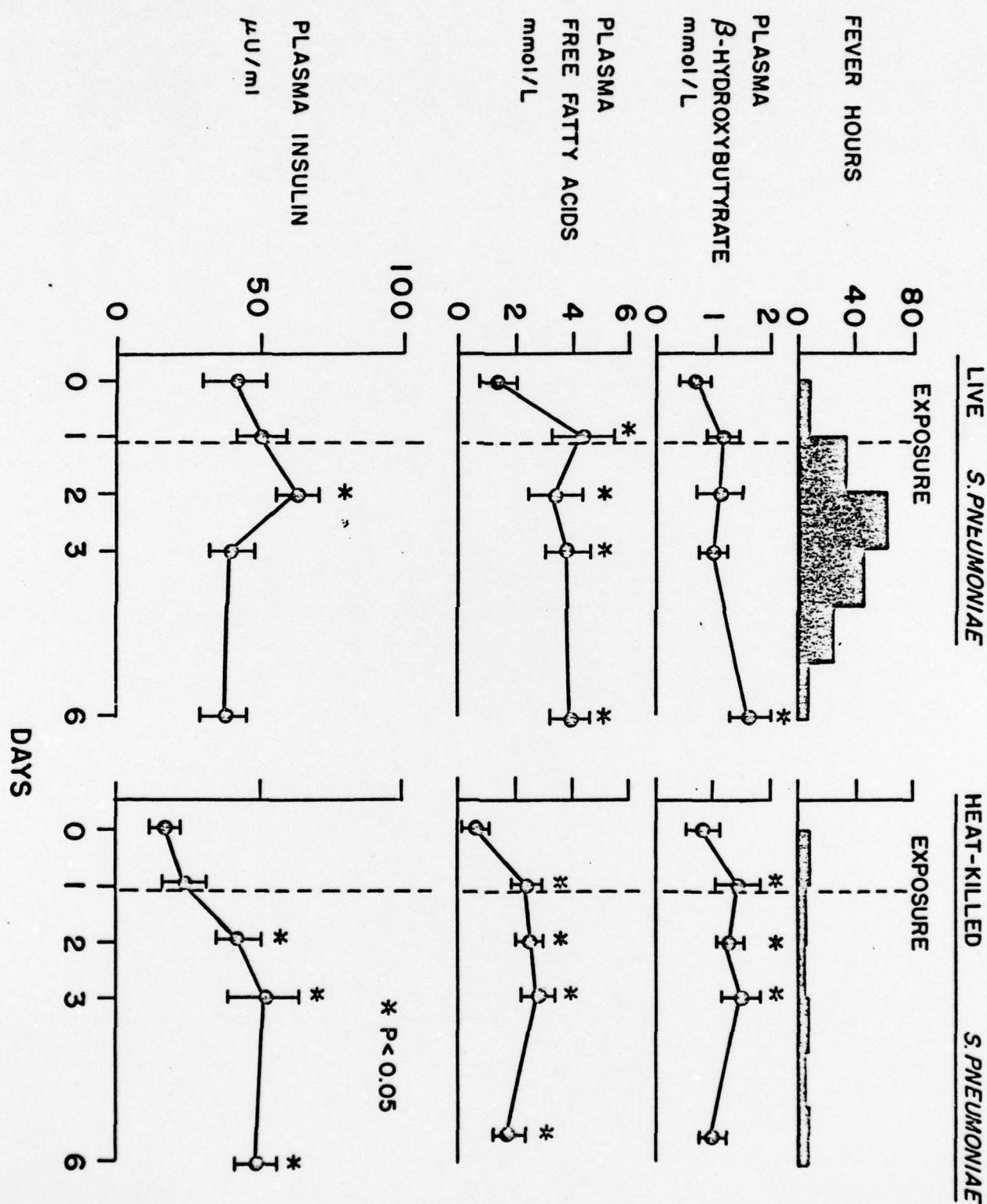


Fig 1



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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A model was developed in the rhesus monkey to determine if the marked wasting of body proteins associated with sepsis could be prevented by an intravenous supply of various nutritional substrates. All monkeys were given a basic infusion of 0.5 g of amino acid nitrogen/kg body weight via an indwelling catheter in the jugular vein. Three groups were given either no added calories, 85 cal/kg from dextrose, or 85 calories from lipid. In each dietary group six monkeys were inoculated with $3 \times 10^8$ Streptococcus pneumoniae and four monkeys, heat-killed organisms. In the monkeys infused with the amino acids alone, pneumococcal		

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sepsis resulted in a four-fold increase in loss of body proteins, compared to calorie-restricted controls. Addition of 85 cal/kg/day of either dextrose or lipid markedly reduced body wasting associated with infectious disease. The calories from lipid were utilized by the septic host as a source of energy, with a slightly reduced efficiency, when compared to the isocaloric infusion of dextrose. The nitrogen sparing of the fat emulsion could not be accounted for by its glycerol content. Therefore, the septic monkey seemed to utilize fatty acids as an energy substrate. It appeared that the carbohydrate calories tended to favor the synthesis of peripheral proteins (associated mainly with skeletal muscle), while lipid calories favored synthesis of visceral proteins, such as plasma albumin and acute-phase proteins.

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